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# The Importance of the Family History in Caring for Families With Long QT Syndrome and Dilated Cardiomyopathy

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In potentially inherited cardiac diseases, the family history is of great importance. We looked at the way cardiologists take a family history in patients with idiopathic dilated cardiomyopathy (DCM) or long QT syndrome (LQTS) and whether this led to screening of relatives or other follow-up. We performed retrospective cross-sectional analyses of adult index patients with DCM or LQTS in a general hospital (GH) or a University Medical Center (UMC). We identified 82 index patients with DCM (34 GH; 48 UMC) and 20 with LQTS (all UMC) between 1996 and 2005. Mean follow-up was 58 months. A family history was recorded in 90% of both LQTS and DCM patients most of the cases restricted to first-degree family members. The genetic aspects, counseling and screening of family members was discussed significantly more often with LQTS than DCM patients (all  $P < 0.05$ ). Also follow-up (screening of family members, DNA analysis and referral) was performed significantly more often in LQTS than DCM patients. Cardiologists in the UMC referred DCM index patients for genetic counseling more often than those in the GH (25% vs. 6%;  $P < 0.05$ ). Only a few index patients with DCM were referred to a clinical genetics department. One-third of DCM cases and nearly all LQTS cases are familial. Since early recognition and treatment may reduce morbidity and mortality we recommend cardiologists take a more thorough family history and always consider referring to a clinical genetics department in such index patients.

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**Key words:** family history; genetics; referral; LQTS; DCM; cardiac disease

## INTRODUCTION

Research into the genetic basis of inherited cardiac disease, including cardiomyopathy and familial arrhythmia, and the increased

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awareness by patients and physicians of their frequent familial origin mean that cardiologists are often confronted with families instead of individual patients [Guttmacher et al., 2004; Charron, 2006; Robin et al., 2007; Cowan et al., 2008; van Spaendonck-Zwarts et al., 2008; Hershberger et al., 2009a].

Idiopathic dilated cardiomyopathy (DCM) and long QT syndrome (LQTS) are increasingly recognized inherited cardiac diseases. DCM is a disease of the myocardium associated with dilation and impaired contraction of the left or both ventricles. It is familial in at least 30% of cases, with an autosomal dominant mode of inheritance being the most common form [Mestroni et al., 1994, 1999; Grünig et al., 1998; Crispell et al., 2002; Burkett and Hershberger, 2005; Kärkkäinen and Peuhkurinen, 2007]. Inherited LQTS is a genetic channelopathy with reduced penetrance that is associated with an increased propensity for ventricular tachyarrhythmias

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and sudden cardiac death in young individuals with normal cardiac morphology. LQTS also generally follows an autosomal dominant pattern of inheritance [Kahn, 2002; Modell and Lehmann, 2006; Goldenberg et al., 2008].

Because of the potential familial character and underlying genetic cause and the potential clinical consequences for family members, obtaining a thorough family history is of great importance [Guttmacher et al., 2004; Morales et al., 2008]. A positive family history enables rapid identification of other affected family members or ones who are at risk for the disease. Early recognition facilitates prevention through early treatment [Hunt et al., 2003; Guttmacher et al., 2004; Cowan et al., 2008; Morales et al., 2008; Hershberger et al., 2009b], especially when sudden cardiac death at a relatively young age can be the initial manifestation [Arnestad et al., 2007; Noseworthy and Newton-Cheh, 2008]. A three-generation family history can help establish a diagnosis in a patient in whom the diagnosis is not completely evident, for example, because of clinical variability and age-related or reduced penetrance, which are not unusual in cardiomyopathies and arrhythmia syndromes like DCM and LQTS [Hunt et al., 2003; Charron, 2006]. A positive family history is important in making decisions about more aggressive treatment of affected family members such as ICD-implantation [Etheridge et al., 2007; Pasotti et al., 2008]. A positive family history for sudden death is also an independent criteria for diagnosing a genetic cardiac disease, for example, arrhythmogenic right ventricular cardiomyopathy (ARVC) [McKenna et al., 1994; Calkins and Marcus, 2008; Hershberger et al., 2009a]. Finally, the family history can provide information on potential genotype–phenotype correlation if the disease-causing gene defect has been identified. Conversely, knowledge of the presentation and development of the cardiac disease in different family members may facilitate research of causative genes [Priori et al., 2003; Goldenberg et al., 2008; Morales et al., 2008].

Despite its demonstrated utility, the accuracy of the family history taken by cardiologists has not been well studied [Guttmacher et al., 2004; Gravely-Witte et al., 2008; Hinton, 2008; Morales et al., 2008]. Little is known about the ability of cardiologists to take a family history and there is no information on what actions cardiologists undertake if they suspect a patient's cardiac disease to have a genetic origin. This means there is little information on how many diagnoses of inherited cardiac diseases are missed. We aimed to assess whether cardiologists in different types of hospitals (a University Medical Center vs. a General Hospital) have a different approach to taking a family history and making a genetic assessment with regard to DCM and LQTS.

## MATERIALS AND METHODS

### Population

Patients, aged 18 years or older who were diagnosed with idiopathic DCM or LQTS between 1996 and 2005 were included. They were diagnosed in either a university medical center (UMC) or a general hospital (GH) in the city of Groningen, the Netherlands. 1996 was selected as the beginning of the study because of the growing

knowledge of DCM and LQTS and the identification of some of the genes related to these disorders since 1996 [Van Spaendonck-Zwarts et al., 2008]. Inclusion up to 2005 provided a reasonable mean follow-up period. Only index patients (the first individual of the family diagnosed) were included. Patients for whom no information on follow-up was available were excluded.

### Recorded Data

In both hospitals, patients with DCM or LQTS were identified using diagnosis-related databases. After verifying the diagnosis and its date, all the relevant information from the medical files was recorded in a separate database. This information was divided into: (1) data concerning the family history actually recorded, and (2) the follow-up assessments after the diagnosis of a potential hereditary cardiac disease. To ensure this information had been recorded accurately in the independent database, 10% of the medical files were randomized and checked by a blinded researcher (J.P. van Tintelen).

### Family History

Analyzed was if a family history was recorded, the degree to which it was obtained (up to third degree) and the various family relationships.

### Consequences/Follow-Up

Each medical file was examined for the period of cardiological follow-up in months and if a positive family history was detected, the subsequent actions were noted. We looked at whether information was discussed with the patient, for example, that the diagnosed (cardiac) disease could be genetic, the possibility of future cardiologic examination and referral to a clinical genetics department. We also looked at whether family members had in fact been examined by a cardiologist, whether DNA analysis had been initiated and whether the patient had indeed been referred to a clinical genetics department.

### Data Analysis

Discrete variables were compared using the Fisher's exact test and are presented as numbers and percentages. Differences between proportions were tested with a 95% confidence interval (CI) [Newcombe and Altman, 2005]. The clinical relevance of the difference between proportions was estimated with Cohen's effect size "h." Effect sizes (ES) were calculated only for the statistically significant results, since differences between groups that were due to random variation have no clinical relevance.

Thresholds of effect size "h" for classifying the magnitude of the differences were: trivial difference ( $<0.20$ ), small difference ( $\geq 0.20$ – $<0.50$ ), medium difference ( $\geq 0.50$ – $<0.80$ ), and large difference ( $\geq 0.80$ ) [Cohen, 1988]. Continuous variables were compared with the Student's *t*-test for independent samples and are presented as means  $\pm$  SD. Statistical analyses were performed using SPSS 12.0.1. for Windows (SPSS, Inc., Chicago, IL).

## RESULTS

### Population

In the UMC and the GH, 188 and 138 patients with DCM were registered, respectively. Fifty and 37 (both 27%) met the criteria for idiopathic DCM, respectively [Mestroni et al., 1999]. Two medical files were not available in the UMC and three in the GH, so that the study population consisted of 48 UMC patients and 34 GH patients (Fig. 1). In the GH no patients with LQTS were registered. In the UMC 162 LQTS patients were registered, 140 of whom were excluded because they were not index patients; they had been referred because of a positive family history. This left 22 patients (14%) (Fig. 1), but two files were missing so the final LQTS population consisted of 20 patients (Fig. 1). The randomized check of 10% of the medical files found no disagreements in the data recorded for our study.

The mean age of diagnosis in the DCM population was 44.2 years in the UMC and 59.0 years in the GH ( $P < 0.01$ ). The age of diagnosis in DCM subjects in the UMC was statistically significant higher than in the LQTS sample (44.2 vs. 30.3 years;  $P < 0.01$ ).

### Family History

A family history was recorded in the medical files of 90% of all LQTS index patients and 90% of all DCM index patients in the UMC. In the GH a family history was taken in 82% of DCM patients (Fig. 1). No significant difference was found between DCM and LQTS patients with regard to the degree the family history was taken; in the UMC the degree to which a family history was taken was recorded for 58% of DCM and for 72% of LQTS patients (ns). In half of these cases, the family history was restricted to first-degree

family members. In the GH, the degree to which the family history was taken was recorded for 50% of the DCM patients; in all cases this was restricted to first-degree family members.

### Consequences/Follow-Up

**DCM versus LQTS in UMC.** In the UMC the mean period of follow-up was 60 months (range: 11–112 months) after the first cardiology consultation for the DCM population, and 54 months (range: 11–107 months) for the LQTS group. This difference was due to random variation (ns) (Table I).

Significantly higher prevalences were measured in the LQTS group compared to the DCM group in the UMC for explaining that the cardiac disease could be genetic, discussing the consequences for family members, discussing referral, cardiology examination of family members, initiating DNA analysis and referral to a clinical genetics department. The differences between LQTS and DCM for “discussing inheritance, discussing the consequences for the family, cardiology examination of family members, and referral” were moderate in size, whilst the differences for discussing referral and initiating DNA analysis were small.

**DCM in UMC versus GH.** Our final groups of patients were small (48 UMC vs. 34 GH patients), however we observed that ten of 48 (21%) DCM patients in the UMC were told the cardiac disease could be genetic compared to 2 of 34 (6%) in the GH ( $P < 0.05$ ). The difference was statistically significant (95% CI 0.01–0.28) but small, according to Cohen’s threshold [1988]. In two UMC DCM cases (4%) DNA analysis was initiated by the cardiologist compared to 0% for the GH patients (ns). Twelve of 48 (25%) UMC DCM patients were actually referred to a clinical genetics department compared to 2 of 34 (6%) of GH patients ( $P < 0.05$ ). This difference

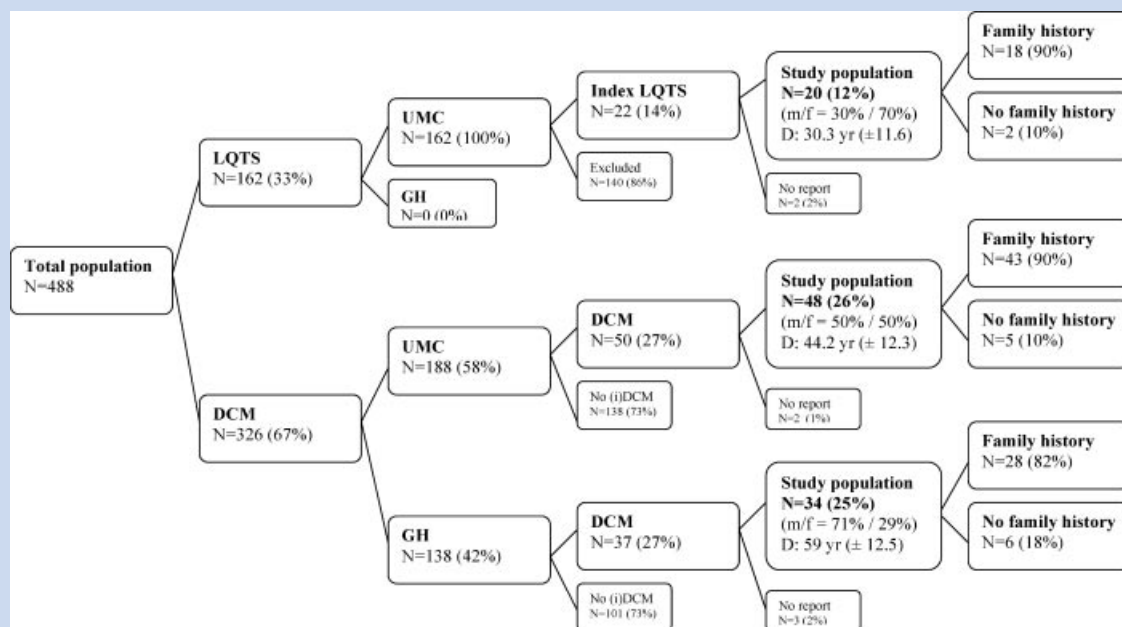


FIG. 1. Subjects: DCM versus LQTS index patients. D, mean age of diagnosis in years; f, female; GH, General Hospital; (i)DCM, dilated cardiomyopathy, idiopathic; LQTS, Long QT syndrome; m, male; UMC: University Medical Center.

TABLE I. Comparison of LQTS and DCM Index Patients in the UMC

	LQTS, N = 20	DCM, N = 48	Difference of proportions test, 95% CI <sup>a</sup>		Effect size
Follow-up in months (SD)	53.6 [29.47]	59.8 [28.93] <sup>b</sup>			n.s.
Family history (%)	18 [90%]	43 [90%]	n.s.		
Discussion:					
Inheritance	15 [75%]	10 [21%]	0.32	0.76	0.51
Consequences for family	11 [55%]	3 [6%]	0.26	0.48	0.55
Referral clinical genetics	8 [40%]	6 [13%]	0.04	0.51	0.31
Cardiologic examination family	12 [60%]	4 [8%]	0.29	0.74	0.55
DNA analysis	7 [35%]	2 [4%]	0.09	0.52	0.41
Referral clinical genetics	16 [80%]	12 [25%]	0.33	0.76	0.51

CI, confidence interval; n.s., not significant.

<sup>a</sup>Newcombe and Altman [2005].<sup>b</sup>Student's *t*-test for independent samples.

was statistically significant but also classified as small. Other differences for DCM index patients in the UMC and GH were not significant (Table II).

## DISCUSSION

One of the most effective measures of a person's risk for a genetic disease is analysis of the family history [Frezzo et al., 2003; Nasir et al., 2007], especially for autosomal dominant cardiac diseases like DCM and LQTS. In addition to helping recognize genetic cardiac disease in the patient, it can help in the early identification of other family members at risk for developing such disease, thereby enabling secondary and tertiary prevention [Hunt et al., 2003; Guttmacher et al., 2004; Cowan et al., 2008; Morales et al., 2008; Hershberger et al., 2009b].

## Study Population

In LQTS, symptoms (like dizziness, fainting, and palpitations) appear on average between 9 and 16 years of age [Zareba et al.,

2003; Goldenberg et al., 2008], whereas symptoms in DCM (like fatigue, shortness of breath) start on average after 30–35 years of age [Mestroni et al., 1999; Burkett and Herschberger, 2005; Hershberger et al., 2009a]. This difference is reflected in the age of diagnosis in our patient groups.

## Family History

Regarding the degree to which the family history taken by the participating cardiologists in the UMC, we saw no differences between the DCM and LQTS index patients. However, for the DCM index patients, cardiologists in the UMC were often more specific in how they took a family history compared to how this was done in the GH. In all cases the family history taken in the GH was restricted to first-degree family members. A family history restricted to first-degree family members can easily result in missing the diagnosis of genetic cardiac disease because of the clinical variability and age-related or reduced penetrance seen in DCM and LQTS [Crispell et al., 2002; Charron, 2006]. A family history well beyond first-degree members and at least three generations is therefore of

TABLE II. Comparison of Cardiologists in the University Medical Center and General Hospital in Their Approach to DCM Index Patients

	UMCG, N = 48	GH, N = 34	Difference of proportions test, 95% CI <sup>a</sup>		Effect size
Follow-up in months (SD)	59.8 [28.93]	51.2 [23.98] <sup>b</sup>			n.s.
Family history (%)	43 [90%]	28 [82%]	−8.2	22.7	0.21
Discussion					
Inheritance	10 [21%]	2 [6%]	0.01	0.28	n.s.
Consequences for family	3 [6%]	1 [3%]	−5.6	12.2	n.s.
Referral clinical genetics	6 [13%]	1 [3%]	−1.4	20.0	n.s.
Cardiologic examination family	4 [8%]	1 [3%]	−4.3	15.1	n.s.
DNA analysis	2 [4%]	0 [0%]	−1.5	9.8	n.s.
Referral clinical genetics	12 [25%]	2 [6%]	4.5	33.7	0.25

CI, confidence interval; n.s., not significant.

<sup>a</sup>Newcombe and Altman [2005].<sup>b</sup>Student's *t*-test for independent samples.



great importance and has recently also been recommended by the Heart Failure Society of America [Hershberger et al., 2009b].

## Consequences/Follow-Up

Perhaps the most important finding was that cardiologists took significantly more often action if they diagnosed LQTS compared to DCM. In particular, cardiologic examination was offered more often to first-degree family members of LQTS index patients than to those of DCM index patients (60% vs. 8%,  $P = 0.00$ ). LQTS patients were also significantly more often referred to a clinical genetics department than DCM patients (80% vs. 25%,  $P < 0.01$ ) (Table I).

It seems cardiologists make more effort to identify family members at risk for LQTS, probably because the genetic knowledge of LQTS is more advanced than for DCM, there is a high risk of sudden death as a first manifestation of LQTS [Arnestad et al., 2007], and LQTS is more likely to have a genetic origin [Goldenberg et al., 2008]. Genetic testing for LQTS has clear benefits for the patient as well as their family members. This is mainly because the choice of therapy largely depends on the genetic subtype. Besides, because of the non-penetrance of ECG characteristics, genetic testing is necessary to identify family members at risk. Subsequent treatment may prevent sudden death [Priori et al., 2003; Goldenberg et al., 2008; Gimeno et al., 2009]. For LQTS genetic testing has been shown to be cost-effective relative to no testing [Phillips et al., 2005].

In DCM the benefit of genetic testing is less clear, because treatment is not dependent on genotype. A possible exception is that carriers of a mutation in the gene encoding lamin A and C (*LMNA*) are believed to be at high risk for sudden cardiac death, justifying ICD-implantation [Meune et al., 2006; van Tintelen et al., 2007; Pasotti et al., 2008]. Sudden death can therefore be a first, yet rare, manifestation of DCM [Noseworthy and Newton-Cheh, 2008]. Despite the fact that DCM has many underlying causes such as myocarditis, coronary disease, alcohol intoxication, or chemotherapy, at least 30% of DCM cases are familial [Mestroni et al., 1999; Kärkkäinen and Peuhkurinen, 2007; Hershberger et al., 2009a]. Cascade genetic testing for DCM will facilitate the recognition of those family members who can be dismissed from regular follow-up screening. Thus, cardiologists must be as attentive in identifying at-risk family members with DCM as compared to LQTS.

Cardiologists in the UMC referred DCM patients to the clinical genetics department significantly more often than those in the GH (25% vs. 6%). This may be due to the cardiogenetic clinic's setting in the UMC, where cardiologists and clinical geneticists regularly consult each other and meet for research purposes. Cardiologists in a UMC may have more knowledge about the inheritance of DCM and LQTS, and the usefulness of DNA analysis in risk stratification.

## CONCLUSION

Although a family history is generally taken by cardiologists, this study shows that follow-up actions (screening of family-members/referral) were performed significantly more often for LQTS than DCM index patients. Cardiologists thus take significantly more effort to identify family members at risk for LQTS in comparison to

DCM. One-third of DCM and nearly all LQTS cases are familial, in which sudden death can be a first manifestation and timely treatment is essential. We recommend that cardiologists take a more thorough family history and always consider referral to a clinical genetics department or cardiogenetics clinics to identify family members at risk.

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